REMARKS

Entry of the foregoing, and further and favorable reconsideration of the subject application, are respectfully requested.

By the present Amendment, p. 1 of the specification has been amended to correct the Continuing Application Data. Paragraphs 20 and 22 of the specification have been amended to insert SEQ ID numbers. Paragraph 71 has been amended to capitalize the trademark "CAPFINDER"TM. Claim 5 has been amended to more precisely recite the claimed invention. Support for the amendments to claim 5 may be found at least at paragraphs 37-41 of the present application. No new matter has been added.

Applicants gratefully note the courtesy shown to their undersigned representative by the Examiner in the telephone conference held on August 9, 2004. In that telephone conference, the renumbering of claims 20 and 21 by the Examiner as claims 38 and 39 was noted and discussed. Applicants' representative agreed to submit the pending claims as determined by review of Applicants' file, subject to correction by the Examiner, while the Examiner agreed that the need for correction of the list of claims would not result in a finding that the present Amendment is not compliant with the Patent Rules.

1. Turning now to the Official Action, Applicants note the statement by the Examiner, at page 2 of the Official Action, that the Restriction Requirement in this case has been made final. Applicants hereby renew their traversal of the Restriction

Requirement, on the bases discussed previously in detail, and respectfully request rejoinder and examination of all the claims of record on the merits.

2. Specification

3. As noted above, by the present Amendment, the Continuing Application Data at p. 1 of the application has been corrected as requested by the Examiner at pp. 2-3 of the Official Action.

4. Drawings

5. As noted above, by the present Amendment, the Brief Description of the Drawings has been amended to insert SEQ ID numbers in the descriptions of Fig 2A and 2C, as requested by the Examiner at p. 3 of the Official Action. Paragraph 71 has been amended to capitalize the trademark "CAPFINDER"TM.

6. Claim Rejections - 35 USC §112

7. At p.4 of the Official Action, the Examiner notes that claims 5-7 are indefinite; this rejection is addressed below. However, it is important to note that, despite the alleged indefiniteness of the claims, the Examiner appears to have arrived at the correct interpretation of the offending limitation (see below).

8. Claims 5-7 are rejected under 35 USC 112, first paragraph as purportedly broader in scope than the enabling disclosure provided by the specification. This amendment is respectfully traversed.

The Examiner concedes, at p. 4 of the Official Action, that the present specification is "enabling for antibody to a Breast Cancer Resistance Protein or BCRP, SEQ ID NO:1." However, the Examiner asserts that the present specification "does not reasonably provide enablement for an antibody to a derivative of Breast Cancer Resistance Protein." Applicants respectfully disagree.

The rejection appears to be primarily based on the recitation of "derivatives" of BCRP in claim 5. At p. 4 of the Official Action, the Examiner notes that "derivatives thereof are not required to induce resistance to cancer therapeutic drugs. This means that the claims are drawn to a whole universe of molecules that would be expected to have neither structural nor functional identity with a Breast Cancer Resistance Protein or BCRP, SEQ ID NO: 1." Applicants disagree, and respectfully direct the Examiner's attention to paragraphs 37-40 of the specification, wherein derivatives of BCRP are explicitly defined.

> **[0037]** The present invention pertains partially to the BCRP, to fragments of this factor, as well as to *functional derivatives*, agonists and antagonists, and metabolic breakdown products of this factor. The BCRP amino acid sequence is depicted in SEQ ID No. 1 and FIG. 2A. The invention especially concerns agents which are capable of inhibiting BCRP, preferably antibodies to BCRP or antisense probes to the BCRP gene. The invention further encompasses chemical agents which inhibit expression of the BCRP gene or mRNA, including Fumitremorgin C (FTC). The invention also concerns methods of inhibiting activity of BCRP or expression of the BCRP gene by administering such agents.
>
> **[0038]** *A "functional derivative" of BCRP is a compound which possesses a biological activity (either functional or structural) that is substantially similar to a biological activity of BCRP.* The term "functional derivatives" is intended to include the "fragments," "variants," "analogues," or "chemical derivatives" of a molecule. A "fragment" of a molecule such as BCRP, is meant to refer to any

> polypeptide subset of the molecule. A functional fragment means that a molecule with a similar, but not identical, amino acid sequence, but has the same function of the full length BCRP. A "variant" of a molecule such as BCRP is meant to refer to a molecule substantially similar in structure and function to either the entire molecule, or to a fragment thereof. A molecule is said to be "substantially similar" to another molecule if both molecules have substantially similar structures or if both molecules possess a similar biological activity.
>
> [**0039**] Thus, provided that two molecules possess a similar activity, they are considered variants as that term is used herein even if the structure of one of the molecules is not found in the other, or if the sequence of amino acid residues is not identical. An "analogue" or agent which mimics the function of a molecule such as BCRP is meant to refer to a molecule substantially similar in function but not in structure to either the entire molecule or to a fragment thereof. As used herein, a molecule is said to be a "chemical derivative" of another molecule when it contains additional chemical moieties not normally a part of the molecule. Such moieties may improve the molecule's solubility, absorption, biological half life, etc. The moieties may alternatively decrease the toxicity of the molecule, eliminate or attenuate any undesirable side effect of the molecule, etc. Moieties capable of mediating such effects are disclosed in Remington's Pharmaceutical Sciences (1980). Procedures for coupling such moieties to a molecule are well known in the art. More specifically, the scope of the present invention is intended to include functional derivatives of BCRP which lack one, two, or more amino acid residues, or which contain altered amino acid residues, so long as such derivatives exhibit the capacity to influence cell resistance to chemotherapy.

(Emphasis added). The present specification further describes, at paragraph 41, that antibodies may usefully be generated to functional derivatives of BCRP.

> [**0041**] A polyclonal antibody capable of binding to BCRP can be prepared by immunizing a mammal with a preparation of BCRP or functional derivative of BCRP. Methods for accomplishing such immunizations are well known in the art. Monoclonal antibodies or fragments thereof can also be employed to assay for the presence or amount or BCRP in a particular biological sample. Such antibodies can be produced by immunizing splenocytes with activated BCRP (7). The BCRP-binding antibodies of the present invention can be administered to patients to reduce resistance to chemotherapy drugs, and hence

> enhance their treatment. Methods of administration will depend on the particular circumstances of each individual patient and are within the skill of those skilled in the art.

(Emphasis added). From the foregoing discussion, one of ordinary skill would understand that the recitation of derivatives does not relate to "a whole universe of molecules that would be expected to have neither structural nor functional identity with" BCRP. Nevertheless, in order to make the claims as clear as possible, claim 5 has been amended to delete reference to fragments, and to explicitly limit the recited derivatives of BCRP to "full-length functional derivatives." As defined in the specification, full-length functional derivatives share both structural and functional characteristics with BCRP. In view of these amendments, Applicants submit that the present claims fully comply with the enablement requirement of 35 USC 112, first paragraph. Withdrawal of this rejection is thus respectfully requested.

9. Claims 5-7 are rejected under 35 USC 112, first paragraph, as purportedly lacking an adequate written description in the specification. This rejection is respectfully traversed.

At page 7 of the Official Action, the Examiner asserts, correctly, that claims 5-7 "are drawn to antibodies that bind to a Breast Cancer Resistance Protein and derivatives, fragments." The present claims are manifestly not drawn to DNA. The Examiner appears to recognize this issue at p. 9 of the Official Action, stating that "a disclosure that does not adequately describe a Breast Cancer Resistance Protein, derivatives or fragments thereof cannot adequately describe the antibodies that bind to said protein, derivatives, or fragments thereof." The Examiner relies for support on

the decisions of the Federal Circuit in *Enzo Biochem, Inc. v. Gen-Probe Inc.,* 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) and *Regents of the University of California v. Eli Lilly and Co.,* 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). However, these decisions both relate to claims to nucleic acids, while the present claims relate to antibodies.

Applicants respectfully direct the Examiner's attention to a more recent decision of the Federal Circuit that deals directly with the question of the written description requirement in the context of claims to antibodies. In *Noelle v. Lederman,* 355 F.3d 1343; 69 USPQ2D 1508 (Fed. Cir. 2004), the Federal Circuit cautioned that "each case involving the issue of written description, 'must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited.'" *Noelle,* 355 F.3d at 1343, *citing Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1562 (Fed. Cir. 1991). The court in *Noelle* found that the application in question, which described and claimed monoclonal antibody to a murine antigen, did not adequately describe monoclonal antibody to mammalian or to human antigen. In that case, no description of any kind of either human antigen, or antigen from any mammal other than mouse, was provided. According to the Court, "Noelle attempted to define an unknown by its binding affinity to another unknown." In contrast, the present claims are directed to antibodies to a protein with a defined sequence – SEQ ID NO:1 – and to "full-length functional derivatives thereof." As discussed above, the structure of those full-length functional derivatives is not unknown; rather, it is clearly defined by reference to SEQ ID NO: 1. As a result, Applicants respectfully maintain that the subject matter of the present claims is adequately described in the present specification. Withdrawal of this rejection is thus respectfully requested.

10. Claims 5-7 are rejected under 35 USC 112, second paragraph, as purportedly indefinite. The Examiner asserts that the claims "are confusing because it is unclear whether the fragments or derivatives thereof are meant to refer to the antibody, a breast cancer resistance protein, or to cancer chemotherapeutic drugs." Despite this apparent confusion, as noted above the Examiner correctly concluded that the offending limitation is meant to refer to the protein. Applicants submit that one of ordinary skill in the art would likewise be lead to the same conclusion. Nevertheless, claim 5 has been amended in order to more explicitly define the claimed invention. Withdrawal of this rejection is thus respectfully requested.

11. Claim Rejections - 35 USC 102

Claims 5-6 are rejected under 35 USC 102(b) as purportedly anticipated by Filipits et al. (1996) *Clin. Cancer Res.* 2:1231-1237; or Dexter et al. (1996) *Proc. AACR* 37:A2138. This rejection is respectfully traversed.

At p. 8, the Examiner asserts that Filipits et al. "teach monoclonal antibodies QCRL-1 and QCRL-3 which both recognize MRP whose expression was observed in all breast cancer specimens assayed and teaches monoclonal antibody C219 which recognizes P-glycoprotein in breast cancer specimens, both of which are breast cancer resistance proteins which induce resistance to cancer chemotherapeutic drugs." However, the antibodies taught by Filipits are not directed to a protein with the sequence of SEQ ID NO: 1, nor to full-length functional derivatives thereof, as those derivatives are defined in the present specification.

Also at p.8, the Examiner asserts that Dexter et al. "teach monoclonal antibodies C219, JSB1, MRK16, UIC2 which recognize MDR1 expression in breast

cancer samples and monoclonal antibodies QCRL1 and MRPm6 which recognize MRP expression in breast cancer samples, both of which are breast cancer resistance proteins which induce resistance to cancer chemotherapeutic drugs. However, the antibodies taught by Dexter et al. are not directed to a protein with the sequence of SEQ ID NO: 1, nor to full-length functional derivatives thereof, as those derivatives are defined in the present specification.

As neither Filipits et al. nor Dexter et al. teach every limitation of the rejected claims, as required by 35 USC 102(b), withdrawal of this rejection is respectfully requested.

13. Claims 5 and 7 are rejected under 35 USC 102(b) as purportedly anticipated by Nakagawa et al. (1992) *Cancer Res.* 52:6175-6181. This rejection is respectfully traversed.

The Examiner asserts that Nakagawa et al. "teach polyclonal antibodies, ASP-14, which binds to P-glycoprotein whose expression was observed in breast cancer cell specimens assayed ... P-glycoprotein is a breast cancer resistance protein which induces resistance to cancer chemotherapeutic drugs." However, the antibodies taught by Nakagawa et al. are not directed to a protein with the sequence of SEQ ID NO: 1, nor to full-length functional derivatives thereof, as those derivatives are defined in the present specification. As Nakagawa does not teach every limitation of the rejected claims, as required by 35 USC 102(b), withdrawal of this rejection is respectfully requested.

14. Claim Rejections - 35 USC §103

15. Claims 5 and 7 are rejected under 35 USC 103 as purportedly unpatentable over Filipts et al. supra or Dexter et al. supra in view of Harlow et al. (1988) *Antibodies: A Laboratory Manual.* Cold Spring Harbor Laboratory Press, p. 142. This rejection is respectfully traversed.

At p. 15 of the Official Action, The Examiner concedes that neither Filipits et al. nor Dexter et al. "teach polyclonal antibody to either the isolated MDR1 or MRP." The Examiner asserts that it would have been obvious, at the time the invention was made, for one of ordinary skill in the art to apply the methods of making polyclonal antibodies taught by Harlow to the teachings of Filipits et al. or Dexter et al. to arrive at the presently claimed invention. However, as noted above, neither Filipits et al. nor Dexter et a. teach an antibody to a BCRP with the amino acid sequence of SEQ ID NO: 1, or to full-length functional derivatives thereof. Thus, even if Harlow teaches a method of making polyclonal antibodies (which Applicants do not concede), the teachings of Harlow do not remedy the deficiencies of Filipits et al. or Dexter et al., in that Harlow does not teach or suggest the amino acid sequence of SEQ ID NO: 1, nor full-length functional derivatives thereof, as required by the present claims. Accordingly, because one of ordinary skill in the art could not combine the teachings of the cited publications to arrive at the presently claimed invention, withdrawal of this rejection is respectfully requested.

16. With regard to the IDS submitted on September 21, 2001, Applicants note that the references appear to have been lost by the Office. Applicants will re-submit the missing references as soon as duplicate copies can be obtained.

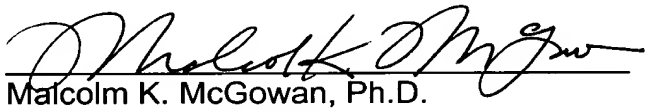
17. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

18. In the event that there are any questions concerning this Amendment, or the Application in general, the Examiner is respectfully urged to telephone Applicants' undersigned representative at the number shown below so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: August 10, 2004

By: 
Malcolm K. McGowan, Ph.D.
Registration No. 39,300

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620